Overlap Syndrome of Autoimmune Hepatitis and Primary Biliary Cholangitis

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KEYWORDS

• Overlap syndrome • Autoimmune hepatitis • Primary biliary cholangitis

KEY POINTS

- Multiple criteria have been used to diagnose and characterize patients with overlap syndrome, including the Paris criteria, the International Autoimmune Hepatitis Group (IAIHG) scoring system, the revised IAIHG scoring system, and the simplified IAIHG scoring system.
- Patients with overlap syndrome have significantly higher rates of portal hypertension, esophageal varices, gastrointestinal bleeding, ascites, death, and need of liver transplant.
- Several retrospective studies comparing treatment with ursodeoxycholic acid alone or in combination with immunosuppression (steroids or a thiopurine) suggest combination therapy may result in improved outcomes.

INTRODUCTION

Over the last 2 decades, there has been increasing attention to a rare clinical subgroup of patients who appear to have a combination of autoimmune liver disease, an "overlap" of conditions such as autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC), that are classically thought to have independent mechanisms. It remains unclear whether overlap syndrome is a variant of PBC, AIH, or an individual entity unto itself, because PBC and AIH share histologic findings, such as ductal injury, which can be seen in AIH, and interface hepatitis, which can be seen as part of PBC.[1,2] The consecutive occurrence of the 2 disorders supports the notion of coincident autoimmune diseases, consistent with the fact that autoimmune disorders are often associated with one another. A series of investigations have attempted to define the affected populations, determine the clinical significance of such presentation, propose diagnostic criteria, and evaluate treatment strategies in this subset of patients. In this review, the authors focus on the overlap syndrome of AIH and PBC (AIH-PBC overlap), highlighting the latest published studies on this topic.

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DEFINITION AND DIAGNOSTIC CRITERIA

PBC-AIH overlap is the most commonly described overlap syndrome, but the term can also be used in reference to overlap of PSC and AIH.[3] Although there is no formal definition of what constitutes PBC-AIH overlap syndrome, the term is typically used to describe patients with clinical features of both antimitochondrial antibodies (AMA)-positive PBC and AIH.[4] The spectrum of presentation and clinical characteristics in individual autoimmune liver diseases has complicated the development of a uniform consensus definition for overlap syndrome.[3] As a result, several distinct criteria have been used to diagnose patients with overlap syndrome of AIH and PBC, including the Paris criteria, the International Autoimmune Hepatitis Group (IAIHG) scoring system, the revised IAIHG scoring system, and the simplified IAIHG scoring system.[5–8]

The Paris criteria were designed to standardize the characterization of patients with AIH-PBC overlap syndrome and are defined by the presence of at least 2 of the 3 accepted key criteria of each disease, as summarized in **Box 1**.[5] It is the most commonly used criteria for overlap syndrome and has been endorsed by the European Association for the Study of the Liver (EASL) and the American Association Society of Liver Disease (AASLD) with the caveat that the histologic finding of interface hepatitis is required to establish the diagnosis of overlap syndrome.[4,9,10]

The original[6] and revised[7] IAIHG scoring systems have also been frequently used to assess for the presence of overlap syndrome in patients with known PBC (the revised IAIHG scoring system is summarized in **Table 1**); however, their effectiveness as diagnostic tools has been questioned.[7] Application of these criteria can be clinically burdensome for the diagnosis of AIH-PBC overlap, given the multiple items required in the scoring system.[7] The scoring systems were also created by an expert panel for the purpose of comparing AIH studies from multiple institutions and to distinguish AIH from PBC, not to diagnose AIH in patients with PBC.[8] As such, both the original and the revised IAIHG scoring systems assign a negative score to the findings of positive AMA or biliary changes on liver biopsy.[11] As a result of the frequent utilization of the scoring systems in the diagnosis of overlap syndrome, the position paper by the

Box 1
Paris criteria

Autoimmune hepatitis

1. Alanine aminotransferase (ALT) ≥5× upper normal limit
2. Immunoglobulin G (IgG) ≥2× ULN or presence of antismooth muscle antibodies
3. Liver biopsy with moderate or severe periportal or periseptal lymphocytic piecemeal necrosis

Primary biliary cholangitis

1. Alkaline phosphatase (ALP) ≥2× upper normal limit or gamma-glutamyl transferase ≥5× upper normal limit
2. Presence of AMA
3. Liver biopsy with florid bile duct lesions

At least 2 of 3 accepted criteria for PBC and AIH, respectively, should be present. Histologic evidence of moderate to severe lymphocytic piecemeal necrosis (interface hepatitis) is mandatory for the diagnosis.

From Chazouilleres O, Wendum D, Serfaty L, et al. Primary biliary cirrhosis-autoimmune hepatitis overlap syndrome: clinical features and response to therapy. Hepatology 1998;28(2):297; with permission.